C. REMARKS

Claims 28-30, 34-37, 41-44, 48-51, 55-58, and 62-77 stood rejected under 35 U.S.C. 102(e) as being anticipated by Abatangelo, et al.

Claims 28, 31-33, 35, 38-40, 42, 45-47, 49, 52-54, 56, and 59-61 stood rejected under 35 U.S.C. 102(b) as being anticipated by Goldberg, et al.

These rejections are respectfully traversed.

The present invention is directed to regenerating meniscal tissue in a joint and thereby to reducing or preventing changes in the joint resulting from meniscal damage, including reducing subchondral bone sclerosis in a joint, preventing or reducing the formation of osteophytes in a joint, and protecting cartilage in a joint of an animal, by injecting into the joint a liquid suspension comprising mesenchymal stem cells and an acceptable pharmaceutical carrier. The mesenchymal stem cells differentiate into and/or stimulate production of meniscal tissue.

The cited prior art is directed to the delivery of mesenchymal stem cells as part of a solid cell-matrix construct to a joint, or to the use of mesenchymal stem cells to treat osteoarthritis. In fact, there is evidence of record, i.e., the Walsh paper, which emphasizes the importance of providing mesenchymal stem cells in a solid implant having sufficient tensile strength. The prior art thus teaches away from Applicants' invention as claimed, wherein a liquid suspension, as opposed to a solid implant, containing mesenchymal stem cells is injected into a joint. Also, in contrast to the cited prior art, such injection of a liquid suspension of mesenchymal stem cells, as claimed by Applicants, prevents osteoarthritis, as opposed to the treatment of osteoarthritis after osteoarthritis has developed.

With respect to the delivery of mesenchymal stem cells in a solid cell-matrix construct to a joint, the Examiner's attention is directed to Walsh, et al., Tissue Engineering, Vol. 5, No. 4, pgs. 327-337 (1999). Walsh was submitted with an Information Disclosure Statement filed on

January 14, 2003. In Walsh, a partial anterior medial meniscectomy was performed in rabbits by resecting the meniscus just anterior to the medial collateral ligament. The rabbits then were left untreated, or were treated with either (i) a periosteal autograft, (ii) a type I collagen sponge, or (iii) a type I collagen sponge loaded with mesenchymal stem cells.

Rabbits were sacrificed 24 weeks after such treatment. With respect to the effectiveness of the treatment of the rabbits with the collagen sponge loaded with mesenchymal stem cells, Walsh, at Page 332, lines 17-19, states:

"However, as in the sponge alone group (group 3), the anterior attachment was not anchored to the intermeniscal ligament in most specimens."

Further, at Page 336, Walsh states, with respect to the collagen sponge implant which includes the mesenchymal stem cells, that:

"As with the sponge alone, in this group there was failure of the anterior attachment, likely due to the lack of tensile strength of the collagen sponge.... It is likely that the inflammatory response caused by the collagen sponge precludes its further use in the joint environment."

(Page 336, lines 1-5).

"The addition of bone marrow-derived mesenchymal stem cells to the collagen sponge enhanced fibrocartilage regeneration in this model. However, the current scaffold lacks initial tensile strength that will provide load-bearing function at the time of implantation. Because the meniscus functions in load bearing by the generation of circumferential tensile stress, the anterior and posterior attachments are of critical importance. These must be secure before significant weight bearing occurs on the regenerated meniscus; otherwise failure is certain."

(Page 336, lines 11-16).

Walsh, therefore, emphasizes the importance of using a solid implant which includes mesenchymal stem cells for regenerating meniscal tissue. Although the collagen sponge loaded with mesenchymal stem cells failed, such failure was not because the collagen was a solid, but because the collagen sponge lacked sufficient tensile strength to become anchored within the joint, and because the collagen sponge elicited an inflammatory response.

Thus, although the collagen sponge failed, and although Walsh provides no specific suggestions as to how to change such failure into success, Walsh emphasizes that in order to regenerate meniscal tissue, one needs to provide mesenchymal stem cells in a solid implant which will be of sufficient tensile strength to become anchored in the joint, and which will not elicit an inflammatory response. Thus, Walsh teaches the need for a solid implant as a carrier for mesenchymal stem cells when regenerating meniscal tissue, and therefore teaches away from Applicants' invention as claimed, whereby mesenchymal stem cells in a liquid suspension are injected into a joint in order to regenerate meniscal tissue.

Abatangelo, like Walsh, discloses a solid cell-matrix construct that contains mesenchymal stem cells.

More particularly, Abatangelo discloses a three-dimensional matrix which comprises an esterified hyaluronic acid and a cell preparation enriched in mesenchymal stem cells. Although Abatangelo uses mesenchymal stem cells in an attempt to repair meniscal tissue, in Abatangelo, the mesenchymal stem cells are in an implant formed from an esterified hyaluronic acid carrier. The implant is prepared, as disclosed in Examples 6 and 7, by loading an esterified hyaluronic acid carrier with a suspension of mesenchymal stem cells. In Example 1, the implant containing the mesenchymal stem cells then is sutured to the remaining lateral meniscus after an anterior medial meniscectomy in the rabbit knee joint.

In Example 7, at Column 14, lines 52-54, it is stated that "The knee joint was carefully dissected and the meniscus harvested and processed for histological analysis." There are, however, no results provided by Abatangelo of such analysis. Thus, Abatangelo provides no evidence that the implantation of the esterified hyaluronic acid carrier containing mesenchymal stem cells resulted in meniscal repair. Even if there were results that did show that the implant of Abatangelo was implanted successfully, the only teaching contained in Abatangelo regarding the regeneration and/or repair of meniscal tissue is to employ a solid implant containing mesenchymal stem cells. Abatangelo, which is directed solely to the implantation of a solid carrier containing mesenchymal stem cells into a joint in an attempt to repair meniscal tissue, does not even remotely suggest to one of ordinary skill in the art that one can repair meniscal tissue by injecting into a joint a liquid suspension of mesenchymal stem cells. Furthermore, Abatangelo, when combined with Walsh, would teach one of ordinary skill in the art to regenerate and/or repair meniscal tissue by using a solid implant containing mesenchymal stem cells, provided that the solid implant has sufficient tensile strength to be anchored to the joint, and that the implant does not elicit an inflammatory response. Thus, Abatangelo and Walsh teach away from repairing and/or regenerating meniscal tissue by injecting into a joint a liquid suspension of mesenchymal stem cells, as claimed by Applicants. Such teaching away clearly is indicative of non-anticipation and non-obviousness. (See W.L. Gore & Associates, Inc. v. Garlock, Inc., 220 U.S.P.Q. 303 (C.A.F.C. 1983), at 312; United States v. Adams, 383 U.S. 39 (1966)).

Thus, Abatangelo does not anticipate Applicants' methods as claimed, nor does Abatangelo render Applicants' methods as claimed obvious to one of ordinary skill in the art.

Goldberg is directed to the administration of mesenchymal stem cells in the treatment of osteoarthritis. Goldberg discloses the use of animal models to induce osteoarthritis, followed by

the administration of mesenchymal stem cells in order to repair articular cartilage damage resulting from osteoarthritis. In one model, i.e., a rabbit model, a partial meniscectomy is performed. This induces osteoarthritis in the rabbit, as well as the cartilage degeneration resulting therefrom.

Goldberg desires to repair articular cartilage damage caused by osteoarthritis by administering mesenchymal stem cells. There is no disclosure or suggestion in Goldberg to repair meniscal tissue as claimed by Applicants.

More particularly, Goldberg's rabbit meniscectomy model is performed in order to induce osteoarthritis and the articular cartilage damage caused by osteoarthritis. The mesenchymal stem cells then are administered in order to determine whether the mesenchymal stem cells will differentiate into cartilage, and thus repair the articular cartilage damage caused by the induced osteoarthritis. Goldberg does <u>not</u> administer the mesenchymal stem cells in order to repair or regenerate meniscal tissue.

By repairing meniscal tissue, Applicants prevent osteoarthritis from occurring. In contrast, Goldberg discloses the administration of mesenchymal stem cells <u>after</u> osteoarthritis has developed, and there is nothing in Goldberg that even remotely suggests to one of ordinary skill in the art that such administration of mesenchymal stem cells after the onset of osteoarthritis results in the repair of meniscal tissue. Goldberg is directed solely to the treatment of osteoarthritis and the repair of articular cartilage damaged as a result of osteoarthritis. Nothing in Goldberg's disclosure would lead one of ordinary skill in the art to expect reasonably that mesenchymal stem cells may be administered to a joint in order to repair meniscal tissue and thus prevent osteoarthritis.

Furthermore, Goldberg's sole objective of regenerating articular cartilage that has been damaged as a result of osteoarthritis is mentioned throughout the Goldberg application, as exemplified by the following passages:

> "Once the condition [i.e., osteoarthritis] has progressed to substantial articular cartilage damage, none of the currently available approaches are adequate."

(Page 3, lines 17-19)

> "The most promising approach to articular cartilage repair appears to be the use of autologous mesenchymal stem cells, which are osteochondral precursors."

(Page 5, lines 18-20)

> "A characteristic indicator of chondral defect is a visibly altered gait or use of the joint to accommodate the discomfort or stiffness resulting from tissue damage, and the objective of treatment is to regenerate full thickness articular cartilage at the site of the defects to thereby prevent the joint destabilization and rapid joint destruction which are common sequelae of advanced osteoarthritis."
>
> "Patients ranging in age from 30-50 years with one or more well-defined articular cartilage lesions (as determined by imaging modalities or diagnostic arthroscopy) are ideal candidates for treatment in accordance with the invention."

(Page 6, lines 15-27)

> "The implants of the invention are indicated for use in regenerating articular cartilage which has been lost through degenerative osteoarthritis."

(Page 11, lines 4-6)

> "Implants containing autologous human mesenchymal stem cells are chondrogenic and, as such, regenerate hyaline cartilage directly at the graft site where they are able to differentiate into cartilage-forming chondrocytes."

(Page 11, lines 10-13)

Regulation of Chondrogenesis

> "This aspect focuses on the identification of molecules regulating mesenchymal stem cells during chondrogenic differentiation, including factors controlling the development of articular hyaline cartilage. To regenerate hyaline cartilage in osteoarthritis patients under a variety of clinical scenarios, it is important to develop a better understanding of the molecules that control the chondrogenic lineage progression of human mesenchymal stem cells."

(Page 17, line 28 – Page 18, line 3)

> ".... 2) once committed, the mesenchymal stem cell-derived progeny cells are capable of progressing toward articular chondrocytes."

(Page 18, lines 13-15)

> "The implant, device and/or composition of the invention utilizes autologous mesenchymal stem cells in a gel, liquid, or molded configuration to regenerate the articular, hyaline cartilage via the developmental course seen during embryonic differentiation."

(Page 30, line 33 – Page 31, line 2)

> "The mesenchymal stem cells in the liquid suspension home directly towards the sites of lesions on the articular surface."

(Page 31, lines 30-32)

> "The ultimate goal of the product development program is to regenerate articular cartilage destroyed by osteoarthritis."

(Page 34, lines 12-14)

Applicants' claimed invention, in contrast, is directed to the repair and regeneration of meniscal tissue. Meniscal tissue is not articular cartilage. Articular cartilage is hyaline cartilage, while meniscal tissue is fibrocartilage. (See Buckwalter, et al., Orthopaedic Basic Science, 2nd Edition, American Academy of Orthopaedic Surgeons, Chapter 17, page 444, column 2, lines 17 and 18, page 445, column 2, line 15 and page 446, column 1, line 6, Table 1, page 445, Figure 3, page 446, and Chapter 20, page 532, column 1, lines 2 and 3. A copy of Chapters 17 and 20 of Buckwalter accompanies this Amendment.)

In addition, as stated previously in Applicants' Amendment filed January 14, 2003, meniscus and articular cartilage have different compositions, structures, and mechanical functions. The major macromolecule in the meniscus is Type I collagen, which has two $\alpha 1$ chains and one $\alpha 2$ chain. (See Adams, et al., Knee Meniscus: Basic and Clinical Foundations, Chapter 2, pages 15-28, Raven Press, Ltd., New York, (1992), a copy of which was submitted with Applicants' Amendment filed January 14, 2003), while the major component of articular cartilage is Type II collagen, which has three $\alpha 1$ chains. (See also, Naumann, et al., J. Histochem. and Cytochem., Vol. 50, No. 8, pages 1049-1058 (2002), at Table 2, page 1053. A copy of Naumann accompanies this Amendment.) In addition, although some Type X collagen is found in articular cartilage, no Type X cartilage has been found in meniscus. Furthermore, meniscus contains significantly less glycosaminoglycans (GAG) than hyaline cartilage. (See Naumann, at page 1053, column 2, lines 17-20 and 32-35, and Table 2.) The collagen content of articular cartilage is about 60% of the dry tissue weight (Mankin, et al., Osteoarthritis, Diagnosis and Medical/Surgical Management, Chapter 5, Moskowitz, et al., Eds., Philadelphia, W.B. Saunders Company (1992), pages 109-154, at page 111, a copy of which was submitted with Applicants' Amendment filed January 14, 2003), while meniscus has a collagen content up to 75% of its dry tissue weight. (See Adams, et al., page 17, column 2, line 27.) The proteoglycan content of the meniscus has been reported to be from about one-twentieth to about one-eighth of that in articular cartilage. (See Buckwalter, et al., at page 534, column 1, lines 25-27 and Adams, et al., page 22, column 2, lines 9-11.)

In addition, articular cartilage is divided into superficial, intermediate, and deep zones; and the collagen fiber orientations and proteoglycan contents vary in each zone. In the meniscus, the collagen fibers predominantly are in a circumferential arrangement, and they act as

reinforcement for the meniscus to resist tensile stresses. (See Adams, et al., pages 19 and 20 and Buckwalter, et al., page 533, column 2, line 35 to page 534, column 1, line 1.)

Also, the stiffness of the meniscus along the collagen fibers (i.e., in the circumferential direction) is one to two orders of magnitude higher than that of articular cartilage. (See Setton, et al., Clinical Orthopaedics and Related Research, number 367S, pgs. S254-S272, Lippincott, Williams & Wilkins, 1999, a copy of which was submitted with Applicants' Amendment filed January 14, 2003). This high stiffness along the collagen fibers enables the meniscus to resist large circumferential stresses that arise when it is loaded. The resistance to fluid flow (which is proportional to the inverse of the hydraulic permeability) of the meniscus is about 6 to 10 times that of articular cartilage, so that the meniscus resists fluid exudation to a greater extent than cartilage.(See Setton, et al., pg. S258, column 2 and pg. S259, column 1, and Buckwalter, et al., pg. 535, column 2, lines 6-9). The lower permeability of the meniscus allows the meniscus to remain pressurized for longer time periods after loading, so the meniscus acts as a fluid-filled cushion. In addition, meniscus has approximately half the elastic modulus of articular cartilage. (See Buckwalter, et al., page 535, column 2, lines 6-9.) Because meniscus and articular cartilage have different compositions, structures, and mechanical functions, Goldberg, which discloses the use of mesenchymal stem cells to regenerate damaged articular cartilage as a result of osteoarthritis, provides no basis for one of ordinary skill in the art to provide Applicants' claimed methods of regenerating meniscal tissue and repairing meniscal damage in a joint.

Because Goldberg does not disclose or even remotely suggest to one of ordinary skill in the art the repair of meniscal tissue by injecting into a joint a liquid suspension including mesenchymal stem cells, Goldberg does not anticipate Applicants' invention as claimed, nor does Goldberg render Applicants' invention as claimed obvious to one of ordinary skill in the art.

Furthermore, the combination of Abatangelo and Goldberg does not render Applicants' method as claimed obvious to one of ordinary skill in the art. While injection of mesenchymal stem cells is taught by Goldberg for repair of articular cartilage in osteoarthritis, Abatangelo clearly teaches the use of solid supports for cell delivery and teaches away from the injection of a liquid suspension of mesenchymal stem cells for repair of meniscal tissue, thereby rendering the injection of a liquid suspension of mesenchymal stem cells non-obvious for meniscal tissue repair.

For the above reasons and others, Abatangelo and Goldberg do not anticipate Applicants' methods as claimed, nor do Abatangelo and Goldberg render Applicants' method as claimed obvious to one of ordinary skill in the art. It is therefore respectfully requested that the rejections under 35 U.S.C. 102 (e) and 35 U.S.C. 102 (b) be reconsidered and withdrawn and a favorable action is hereby solicited.

Respectfully submitted,

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